AJAY VERMA, MD, PHD

NEUROMUSCULAR AND NEURODEGENERATIVE DISEASES

INTRODUCTION: The nervous system can be segregated into subsystems such as the peripheral and central nervous system. These are further segregated into functional substructures such as motor and sensory systems, motor units, upper and lower motor neurons, etc. This means of categorization is very useful for understanding the physiology and pathophysiology of the nervous system. The nervous system is also made up of several different cell types, which display distinct functions and distinct pathological reactions. Neurons and glia are the distinctive cells of the nervous system and are each further differentiated into unique cell types such as sensory-, motor-, and inter-neurons or astrocytes, Schwann cells and oligodendrocytes. The resulting cell specialization reflects itself in both form and function. Thus, unique molecular and structural elements are seen in each type of specialized cell in the nervous system. Pathological reactions of the different cell types are reflective of these specializations. Muscle cells are also subspecialized into striated (skeletal, cardiac) and smooth muscles cells with obvious functional and structural differentiations. Skeletal muscle cells can be further distinguished by unique metabolic and functional features. Recognition of these features is useful in understanding neuromuscular disease. Neurons and striated muscle cells are postmitotic cells that, once differentiated, are meant to last a lifetime. This leads to unique responses to injury that differ from most other cells. Among these responses are unique cell and tissue reactions that can, at first be confusing for medical students. This lecture will focus on selected neuromuscular and neurodegenerative diseases in an effort to elucidate key pathological and pathophysiological concepts in neuropathology.

THE MOTOR UNIT CONCEPT:

Muscle fibers, neuromuscular junction, axon with myelin sheath, anterior horn motor neuron cell.
All skeletal muscle fibers of a motor unit are innervated by a single motor neuron.

The Skeletal Muscle Fiber:

Syncytial cells. Peripherally located Nuclei. Contractile apparatus (myofibrils = sarcomeres laid end-to-end). Contractile proteins of sarcomere- Actin (thin filaments), Myosin (thick filaments).
Metabolic machinery (inter-myofibrillary network)
T-tubules- sarcolemmal membrane invaginations that facilitate action potential conduction to interior of fiber. Endoplasmic reticulum (sarcoplasmic reticulum) - calcium storage. Calcium couples membrane depolarization to sarcomeric contraction.
Energy sources (glycogen, lipid). Mitochondria.

Skeletal Muscle Fiber Types
Type I fibers (S low-twitch) repetitive, sustained contraction; oxidative; “red meat”
Type 2 fibers: 2b - Fast-twitch; short, intense contraction; glycolytic, “white meat”;
2a - Hybrid; oxidative and glycolytic.
A given fiber’s type is determined by motor innervation and all fibers belonging to a single motor unit are of the same type. Motor units intermeshed in normal muscle, producing random checkerboard pattern of type I and type 2 fibers. Fiber type can be distinguished in biopsies through special staining procedures.

Skeletal Muscle Disorders:

Denervation atrophy: Atrophy of muscle fibers resulting from loss of axonal contact
Helps distinguish primary muscle disorder from other disorders as cause of weakness.

Primary myopathies:

A. Inflammatory myopathies: Autoimmune damage to skeletal muscle

Dermatomyositis:
Clinical: Symmetrical proximal muscle weakness in adults and children;“heliotrope” rash; association with visceral malignancy in adult women
Laboratory: Elevated serum creatine kinase (CK)

Etiology: Antibody and complement attack on muscle capillaries
Biopsy: Muscle fiber degeneration, phagocytosis, and regeneration; with perivascular lymphocytes.
Treatment: Corticosteroids and immunosuppressives

2. Polymyositis

Clinical: Symmetrical proximal muscle weakness without rash
Laboratory: Elevated serum creatine kinase (CK)
Etiology: Cell-mediated immune attack on muscle fibers by cytotoxic lymphocytes
Biopsy: Muscle fiber degeneration, phagocytosis, and regeneration with endomysial lymphocytes attacking individual muscle fibers
Treatment: Immunosuppression

B. Non-inflammatory myopathies

1. Muscular Dystrophies: Often classified by mode of inheritance.

- X-linked "Dystrophinopathies": Duchenne's Muscular Dystrophy (DMD) and Becker's Muscular Dystrophy (BMD)
- Autosomal dominant: Myotonic Dystrophy

a. Duchenne's muscular dystrophy (DMD)

Clinical: Affects males; normal at birth; onset of pelvic girdle weakness by age 5. Calf pseudohypertrophy. Wheelchair bound by 12. Death by early 20's.
Laboratory: Elevated serum CK (until late stages)
Etiology: Lack of dystrophin, a muscle fiber protein that maintains integrity during contraction. Encoded on X chromosome (Xp2l)
Biopsy: Wide range in muscle fiber size from atrophic to hypertrophic, Myofiber degeneration, phagocytosis, regeneration. Interstitial (endomysial) fibrosis and infiltration. No or minimal inflammation.

b. Becker's muscular dystrophy (BMD)

Clinical: Affects males; normal at birth; later onset than Duchenne's with slower progression and longer survival
Laboratory: Elevated serum CK
Etiology: Abnormal dystrophin molecule that is not fully functional
Biopsy: Similar to Duchenne's but findings are less severe

c. Myotonic Dystrophy

Autosomal dominant trait localized to chromosome 19q13.2-13.3
Most common adult muscular dystrophy
Clinical: Myotonia (involuntarily delayed muscle relaxation after contraction) Phenotypic abnormalities: frontal baldness, cataracts, muscle weakness and atrophy with characteristic facies, gonadal atrophy, cardiac and smooth involvement, mental retardation. Onset: Childhood to adulthood; may also be congenital
Laboratory: CK may be normal or elevated
Etiology: Expanded tandem trinucleotide (CTG) repeat in gene for myotonin protein kinase (chromosome 19q)
Biopsy: Variable myofiber degeneration, phagocytosis, regeneration
Increased internally positioned nuclei, often in long rows
Aberrantly positioned, circumferentially arranged myofibrils

2. Congenital Myopathies

Group of loosely related diseases characterized by a congenital abnormality muscle fiber structure leading to a recognizable pathologic pattern on biopsy.
Myopathies named according to distinctive pathologic pattern

- Central core myopathy
- Nemaline myopathy
- Centronuclear myopathy

Clinical: Onset at birth or in infancy, Non-progressive or slowly course, Proximal or generalized muscle weakness. Hypotonia ("floppy baby") or Joint contractures (arthrogryposis).

3. Metabolic Myopathies
Muscle diseases resulting from a defect in muscle fiber energy production.
a. Glycogenoses: Glycolytic enzyme deficiency; example: McArdle's disease (myophosphorylase deficiency)
b. Lipid myopathies: Defect in lipid transport across inner membrane: carnitine and carnitine-palmitoyl transferase (CPT) deficiency
c. Mitochondrial myopathies: Deletion or point mutation in mitochondrial nuclear DNA, leading to mitochondrial enzyme defect; biopsy may show increased numbers of (or enlarged) mitochondria which appear as abnormal aggregates at the light microscopic level ("ragged red fibers"); example: Kearns-Sayre syndrome (external ophthalmoplegia, pigmentary retinal degeneration, heart block)

4. Toxic Myopathies
May be secondary to endocrinopathies; examples: hyper- or hypothyroidism; External toxins: ethanol; Therapeutic drugs: corticosteroids, chloroquine, anti-retrovirals

The Neuromuscular junction: Synaptic connection between motor axon presynaptic ending and skeletal muscle. Site of conversion of electrical neuronal transmission into chemical signal to initiate muscle cell depolarization. Key components: presynaptic calcium channels, synaptic vesicles containing the neurotransmitter acetylcholine, synaptic cleft with acetylcholinesterase, postsynaptic muscle membrane with nicotinic acetycholine receptors.

Neuromuscular Junction Disorders:
1. Myasthenia gravis (MG)
Clinical: adults; female preponderance in patients younger than 40
Muscle fatigues on repeated contraction, Extraocular muscle involvement. Temporary improvement with anticholinesterase agents (Tensilon test)
Laboratory: ACh receptor antibody in serum
Electromyography: Rapid reduction in amplitude of muscle action potential with repetitive stimulation ("decrementing response"), reversed by anticholinesterase agents
Etiology: IgG autoantibody blocks and destroys post-synaptic ACh receptors
? Role of thymus: Source of cross reacting antigens or CD4+ cells to stimulate autoantibody?
Thymic hyperplasia - 65-75 percent of MG patients. Thymoma - 10-15 percent of MG patients
Biopsy: No denervation atrophy. Endomysial lymphocyte collections and type 2 fiber atrophy
Treatment: Anticholinesterase agents, Corticosteroids, plasmapheresis in crisis, Thymectomy

2. Lambert-Eaton Myasthenic Syndrome (LEMS)
Paraneoplastic complication (small cell lung carcinoma), Autoimmune IgG attack on presynaptic membrane calcium channels. Decreased release of ACh in response to nerve depolarization.
Clinically differentiated from Myasthenia Gravis
- Muscle does not fatigue with repeated contraction
- No improvement after anticholinesterases Electromyography
- Amplitude of muscle action potential increases with repetitive stimulation

3. Botulism
Bacterial toxin *(Clostridium botulinum)* blocks presynaptic Ach release
C. *botulinum* is an anaerobe. Improper sterilization of canned food. Wound infection.
Treatment: Respiratory support, Antitoxin administration.

Peripheral Neuropathies:

1. Axonal Degeneration
Wasting away of axon (with or without neuronal cell body) with secondary myelin sheath disintegration.
Etiologies: Toxic (hexane), metabolic (diabetes, uremia), nutritional deficiency (thiamine), infectious (HIV), hereditary, paraneoplastic, idiopathic. Usually starts at distal end of axon and

advances centripetally (“dying back”). Usually involves both sensory and motor fibers, often affecting longest and largest-diameter fibers first

- Sensorimotor polyneuropathy
- “Stocking and glove” distribution

Axonal regeneration possible if etiologic condition reversed

2. Segmental Demyelination

Myelin sheath or Schwann cell (rather than axon) primary target of pathologic process
Usually immune-mediated; Humoral (B-cell) or cellular (T-cell) effectors of immunologic insult. Monocyte/macrophage system removes damaged debris. Damaged myelin reconstituted by Schwann cell. Axonal degeneration if myelin sheath disruption is severe or prolonged. Clinical evolution may be short (days).

a. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) "Guillain-Barre Syndrome"

Clinical: Often preceded by immunologic challenge. Rapidly progressive (days) ascending motor weakness. Sensory symptoms milder than motor. Spontaneous resolution after days, weeks, or months in most cases.

Laboratory: CSF: elevated protein, normal cells = “cell-protein dissociation"
Electromyography/Nerve Conduction Velocity (EMG/NCV) study: Nerve conduction velocity slowed or blocked.

Treatment: Mechanical ventilation if respiratory muscles paralyzed. Plasmapheresis in severe cases, ie. respiratory failure, bulbar involvement.

b. Chronic inflammatory demyelinating polyradiculoneuropathy (AIDP)

Relapsing and remitting form

Motor neuron diseases ("lower motor neuron"):

1. Acquired: Viral, toxic

a. Poliomyelitis (Acute anterior poliomyelitis)

Polio, Coxackie, and other enteroviruses. Virus enters body through GI tract, multiplies in gut lymphoid tissue, and spreads to CNS through blood. Spread by oral-oral and oral fecal routes. Virus infects large motor neurons of the spinal cord and brainstem.

Clinical: Viral illness (sore throat, GI upset, mild fever, malaise, headache), followed in just 1-2% of such cases with neurological involvement. Muscles become flaccid and weak with atrophy.

Treatment: immunization

b. Post-polio syndrome:

New onset weakness and fatigue many years after recovery from acute paralytic poliomyelitis. Essentially a "wearing out' of surviving motor neurons which were supporting muscle fibers initially denrvated upon death of polio-virus infected motor neurons.

2. Inherited: Several spinal muscular atrophies, Component of other neurodegenerative diseases.

a. Spinal muscular atrophies (SMA):

Proximal:

- Type I: Acute infantile (Werdnig-Hoffman disease)
- Type II: Late infantile; Juvenile (Kugelberg-Welander disease)
- Type III: Adult

Regional: Several types: progressive muscular atrophy (PMA), and progressive bulbar palsy (PBP) are thought to be similar conditions, bulbospinal, distal, oculopharyngeal, etc.

THE UPPER MOTOR NEURON CONCEPT:

Motor units are regulated by local reflexes for reflexive movements and by inputs from "higher center" for various conscious and unconscious movements. The voluntary, finely controlled movements which allow us to express ourselves require the regulation of motor units by the pyramidal tract but also by the vestibular, cerebellar, and basal ganglia systems. Traditionally, the pyramidal tract neurons originating in the primary motor cortex are referred to as "upper

motor neurons". Diseases affecting these cells, their axons or their myelin sheath will all result in weakness. Disorders of basal ganglia or cerebellar structures do not produce weakness per se but severely compromise voluntary and involuntary movement.

Diseases involving upper and lower motor neurons:

1. Neurodegenerative disease: strike at the neuron
a. Amyotrophic lateral sclerosis (ALS): "Lou Gehrig disease"
Clinical: A neurodegenerative disease which presents with muscle weakness, usually in distal extremities, more or less symmetrical. Weakness progresses to involve whole body. ALS effects both upper and lower motor neurons. Average duration of disease is 3-5 years
Lower motor neuron symptoms: muscular atrophy, fasciculations, weakness
Upper motor neuron symptoms: hyperreflexia, spasticity, Babinski reflex.

Pathology: Gross: shrunken, gray, anterior nerve roots, atrophy of spinal cord (lateral columns). Microscopic: Loss of motor neurons with gliosis in spinal cord, brain stem, motor cortex. Inclusions seen with H&E in neuronal perikarya : Bunina bodies=2-5μm eosinophilic beaded chains; large hyaline inclusions; slightly basophilic inclusions; Axonal spheroids; Balloned neurons; Ubiquitin inclusion bodies
Etiology: 5-10% of cases are familial (FALS)-AD; Present 10 years earlier than sporadic disease; Linkage between FALS and chromosme 21 in region of Cu/Zn superoxide dismutase (SOD1)

2. Disease affecting myelin component of upper motor neurons:
a. Vitamin B12 deficiency:
Vitamin B12 deficiency caused by dietary deficiency, pernicious anemia, gastric surgery.
Clinical: Insidiously progressive neurologic symptoms including weakness.
Pathology: Subacute combined degeneration of the cord, peripheral neuropathy, dementia, and optic atrophy. Affects myelin synthesis in BOTH Shwann cells and Oligodendrocytes
b. Demyelinating disease: The definition of demyelination is the destruction of myelin with relative presentation of axons and is a process exclusive to the central and peripheral nervous systems. Some demyelinating diseases only affect peripheral, Schwann cell-elaborated myelin (as seen for Guillan-Barre syndrome above) while others only affect central, oligodendrocyte-elaborated myelin (as with multiple sclerosis). Others affect both. While viruses (progressive multifocal leukoencephalopathy, HIV- 1), inherited storage disorders (metachromatic leukodystrophy, Krabbe's disease, adrenoleukodystrophy), toxic disorders (central pontine myelinolysis, diabetes), and postinfectious disorders (Guillan- Barre syndrome, postinfectious encephalomyelitis) can all cause demyelination, the number one demyelinating disorder is multiple sclerosis.

Multiple sclerosis:
Clinical, epidemiological, and genetic features: Predilection of MS for females, young adults, Caucasians, temperate climates, HLA type, increased risk in-family members. Autoimmune factors important as suggested by similarity between MS and EAE. Multiple CNS lesions in space and time give varied clinical features; relapsing and remitting illness. Multiple sclerosis (MS) primarily impacts people during their most productive and childbearing years, ages 20-40. Like autoimmune disorders in general, it is most common in females and affects higher socioeconomic classes, Caucasians, and college-educated individuals. Distinct geographical variation in incidence suggests exposure to an environmental agent(s) prior to age 15 may be epidemiologically important. High risk areas include temperate climates, especially northern Scotland; it is uncommon in the southern hemisphere and is rare in Japan and the tropics. Emigration from a high risk to low risk area before age 15 reduces the risk for MS. Genetic factors play a role. Some races are not susceptible to MS despite the latitude at which they live. Also, twin studies sugges greater incidence in monozygotic than dizygotic twins. Histocompatibility antigens (HLA) on chromosome 6 control the immune system, and innorthern ~urope~HLA types DW2 and DR2 are

associated with MS. In Japan, HLA BW22 and DRG are associated, but HLA
Pathology: Primary demyelination in the CNS with relative axonal sparing. Periventricular and perivenular predilection for plaques. Acute, chronic active, chronic inactive plaques. Clinical and pathologic variants.

SUBCORTICAL NEURODEGENERATIVE DISEASES

1. Parkinsonism and Idiopathic Parkinson's Disease

Clinical: Movement disorder with tremor, rigidity, akinesia; dementia. Common presentations: decreased facial expression, rigidity, stooped posture, slow voluntary movements, pill rolling tremor, festinating gait, autonomic dysfunction, dysphagia, cognitive difficulties. Symptoms related to decreased dopaminergic input to striatum secondary to degeneration of neurons in pars compacta of substantia nigra.
Etiology: Idiopathic- no etiology known, most common. Post-infectious-von Economo's encephalitis (1918-1920). Toxic- CO, manganese intoxication, phenothiazine toxicity, MPTP (1-methy-4 phenyl-1,2,3,6-tetrahydropyridine)
Pathology: Damage to dopaminergic substantia nigra pars compacta as well as to noradrenergic, serotonergic, and cholinergic systems.Lewy bodies in pigmented and nonpigmented brainstem, subcortical, and cortical neurons
Nigrostriatal system diseases: Parkinson's disease, striatalnigral degeneration, Shy-Drager syndrome, progressive supranuclear palsy
Lewy bodies: Lewy bodies must be found to diagnose Parkinson's disease. These are eosinophilic cytoplasmic inclusion in neurons in SN, locus ceruleus, cortex and elsewhere. Marker proteins: alpha synuclein, NFP, ubiquitin, αB crystallin, tubulin, MAPs, APP, synaptic proteins.
Ultrastructure: amorphous electron dense core, peripheral filaments, lipofuscin, neuromelanin, mitochondria

2. Huntington's Disease

Clinical: Dementia and choreiform movements; autosomal dominant gene with 100% penetrance on chromosome 4. Autosomal dominant. Incidence 4-7/100,000. Usually presents around 4th decade. Average life span after presentation 14-17 years.
Common presentation: abnormal involuntary movements, cognitive difficulties, memory loss, depression, irritability, sometimes rigidity or abnormal eye movements
Pathology: Gross: atrophy (decreased weight of brain), atrophy of caudate and putamen, ventricular dilatation. Earliest changes in medial caudate, tail of caudate, and dorsal putamen. Microscopic: Profound degeneration and loss of neurons in caudate and putamen. Heavy loss of medium sized spiny (GABAergic, enkephalinergic, and substance P) neurons-neurons that project to substantia nigra and medial and lateral sections of globus pallidus
Genetics: HD gene on chromosome 4p, encodes gene huntingtin. Huntingtin found in many tissues, unknown function. Huntingtin gene has CAG repeat (normal 9-37). >40 CAG repeats is increased risk. Anticipation
Pathogenesis: loss of striatal inhibitory output.

CORTICAL NEURODEGENERATIVE DISEASES

1. Alzheimer's Disease

Economic/medical importance:

- approximately 5 million Americans have AD, projected that 14 million Americans will have AD by 2050
- 1/10 >65 years and 5/10 > 85 years old have AD
- U.S spends at least $100 billion/year on AD
- average lifetime cost/patient with AD $174,000
- lifespan with AD 8-20 years
- third after heart disease and cancer for expense to society

- federal government spends $1 for research for every $324 disease costs (heart disease, cancer and AIDS funding 4-7x more)

Epidemiology:
50-75% of cases of dementia in adults, male:female about 1:1; incidence increases with age; most cases are sporadic; % have strong family history; Down's Syndrome

Clinical presentation:
- Memory difficulties
- decline in intellect
- mood and behavioral changes
- disorientation
- late immobile, mute

Pathology: Gross exam: atrophy, 900-1200 grams, widened sulci, narrow gyri. Microscopic exam: neurofibrillary tangles, neuritic plaques, neuropil threads, amyloid angiopathy, Hirano bodies, granulovacuolar degeneration

Neurofibrillary tangles: Neuronal cytoplasmic inclusions, very insoluble. Basophilic, flame to globose shape (depends on shape of neuron). Predominantly hyperphosphorylated tau protein; tau protein involved in microtubule assembly
Ultrastructurally composed of paired helical filaments (PHFs)-tau, MAP2, ubiquitin, Aβ amyloid. Not specific for AD, also seen in Progressive supranuclear palsy, post-encephalitic Parkinson's disease, ALS-PD Guam

Neuritic Plaques: Found in cortex, deep gray matter, and cerebellum; Composed of extracellular proteinaceous deposits (predominantly AB peptide) and abnormal neuritic processes; Dystrophic neurites are abnormally dilated neuronal processes; Amyloid core stains with Congo red, Bielschowsky, thioflavin S; Associated microglia and astrocytes

Amyloid precursor protein: Normal transmembrane glycoprotein; Chromosome 21; Function unknown; Aβ peptide in plaques is 42-43 residue derived from APP; Cleavage by three enzymes: α-secretase:cleaves APP near center; β-secretase: cleaves APP near N-terminus; γ-secretase: cleaves APP by C-terminus

Neurochemistry: Loss of cholinergic input; loss of neurons in nucleus basalis of Meynert

Alzheimer's disease genes: APP on chromosome 21; ApoE on chromosome 19; Presenilin -1 (PS-1) on chromosome 14; Presenilin -2 (PS-2) on chromosome 1.

Amyloid angiopathy: Amyloid deposited in parenchymal and arachnoid vessels in 90% of patients with AD; Vascular amyloid is predominantly Aβ-39/40 instead of Aβ42/43 found in plaques; Amyloid angiopathy predisposes to hemorrhage

Special thanks to Dr. Kondi Wong and Dr. Alan Morrison of the AFIP for their help with this handout.